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VITAMIN B_{12}

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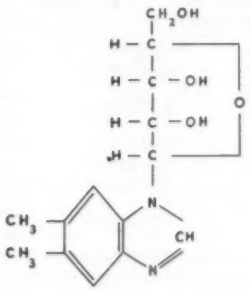
Isolation. Vitamin B_{12} was not isolated until more than 20 years after Minot and Murphy [1] had first shown the efficacy of liver in the treatment of pernicious anaemia. In the meanwhile many vitamins had been identified, usually within a few years of the first realization of a specific deficiency.

There is a number of reasons why vitamin B_{12}, the effective liver principle, so long defied the efforts of many investigators. Until a very short while before its almost simultaneous purification by independent teams of workers in the U.S.A. and England (Rickes *et al.*,[2] Smith [3]) there was only one test available, assessment of clinical improvement of pernicious anaemia patients in relapse. These tests are difficult and laborious and only few patients are available for them. Vitamin B_{12} is extremely active (10 μg per fortnight are sufficient to maintain some patients); even in liver, until recently the richest known source, it occurs in concentrations of only about one part per million. These facts proved considerable obstacles to progress and it was only by the application of the recent elegant technique of partition chromatography that Smith was finally able to isolate the vitamin in the crystalline state.

Vitamin B_{12} Group. Smith [4] had early obtained two different impure red fractions, both of which were effective in controlling pernicious anaemia. One of them was later shown [3] to owe its activity to vitamin B_{12}. More recently three other compounds, all very similar in chemical and physical properties and approximately as active as B_{12}, have been characterized. B_{12a}[5] is a chemical reduction product of B_{12} itself; B_{12b} is isolated from fungal fermentation liquors [6] and may also be produced from B_{12} by reduction. B_{12a} may indeed prove to be identical with B_{12b}. A further closely related substance, provisionally called B_{12c}, has recently been isolated by Smith [7] in the Glaxo Laboratories from liquors obtained during the production of streptomycin by the fungus *Streptomyces griseus*. All four of these active substances have closely similar physical and chemical properties. B_{12} itself has a molecular weight of about 1500 and, like the other associated factors, contains cobalt and phosphorus as well as carbon, hydrogen, oxygen and nitrogen. All are very readily destroyed by alkali but are relatively stable under slightly acid conditions (pH 4 – 7). Very little is yet known of their chemistry but from a study of its breakdown products [8-10] it is known that the B_{12} molecule contains the grouping shown in Fig. 1:—



Vitamin B_{12} contains a phosphate grouping known to be combined at either the 2 or 3 position in the ribityl moiety of the molecule.

FIG. 1

It is of interest to notice the similarity between the chemical constitutions of this fragment of the B_{12} molecule and of riboflavine.

Functions of the Vitamin. Vitamin B_{12} is essential for the growth of certain bacteria (e.g. *Lb. lactis and Lb. Leichmannii*) and animals (pig, chicken, turkey) and may be used in the treatment of a number of human macrocytic anaemias.

PERNICIOUS ANAEMIA

Pernicious anaemia can be controlled by large doses of liver given orally or by injection of suitable liver extracts. These extracts are not effective when administered by mouth (other than in very large amounts) and their activity has been shown to parallel their vitamin B_{12} content.

In a series of skilfully devised clinical experiments (reviewed by Ungley [11]), Castle and his collaborators showed that pernicious anaemia could not be controlled by the oral administration of beef muscle, whereas if beef muscle (or extracts) were first digested with gastric juice from normal patients, then satisfactory

responses could be obtained by oral administration. From this work Castle postulated the presence in food of a substance, the extrinsic factor, which combines with a substance in normal gastric juice, the intrinsic factor, to form the effective substance, the liver principle, which is stored in that organ.

B_{12} is ineffective when given orally (except perhaps in enormous doses) but its incubation with normal gastric juice gives an effective product like the postulated extrinsic factor.[12] Thus B_{12} has been shown to be identical with, or behave as, both the extrinsic factor and the liver principle. It is therefore probable that the intrinsic factor is essential for the absorption of B_{12} and that pernicious anaemia patients suffer from B_{12} deficiency because of inability to produce this intrinsic factor. This supposition may be supported by the observation[13] that large amounts of B_{12} are excreted in the faeces of pernicious anaemia patients.

Table I shows the effects of B_{12}, beef muscle extracts and gastric juice on pernicious anaemia and the way in which the mode of administration affects the results obtained.

TABLE I

Substances	*Mode of Administration*	*Clinical Result*
B_{12}	Parenteral	Effective
B_{12}	Oral	Ineffective
B_{12} and pernicious anaemia gastric juice	Oral	Ineffective
B_{12} and normal gastric juice	Oral	Effective
Beef muscle digest extract	Oral	Ineffective
Beef muscle digest extract	Parenteral	Partially effective
Beef and pernicious anaemia gastric juice	Oral	Ineffective
Beef and normal gastric juice	Oral	Effecitve
Folic acid	Oral or parenteral	Controls haematological but not neurological conditions.

The observation that beef muscle extracts are not completely effective by injection may be related to the technical difficulty of preparing suitable extracts, or it may be that there is present another form of B_{12} that is not active by injection but may become effective after digestion.

Ternberg and Eakin[14] have shown that normal gastric juice contains a heat-labile substance that can combine with B_{12} and render it unable to promote bacterial growth. One ml. of gastric juice from a normal person can combine with about 60 mμg of B_{12}, whereas 1 ml. gastric juice from a pernicious anaemia patient will only combine with about 5 mμg B_{12}. It is very probable that the intrinsic factor is similar to or identical with this heat-labile substance. Further work is required to elucidate all these matters.

Relation between Folic Acid and B_{12} in Pernicious Anaemia. Pernicious anaemia is characterized by a megaloblastic bone marrow, a macrocytic anaemia and absence of hydrochloric acid and intrinsic factor from the gastric juice. If the condition is not adequately treated the symptoms of subacute combined degeneration of the spinal cord (S.C.D.) will sooner or later become apparent and will increase if already present. Folic acid orally or by injection will control the anaemic symptoms but even in large doses will not control or prevent the onset of S.C.D.

Isolated megaloblastic bone marrow cells from pernicious anaemia patients rapidly assume a normal appearance when treated with folic acid.[15] B_{12}, however, will not bring about this effect.[16] In spite of these observations parenteral B_{12} will, like folic acid, cause the megaloblastic bone marrow of pernicious anaemia patients to assume a normoblastic appearance within 72 hours. Furthermore the amounts of B_{12} required are about 1/1,000th of the amounts of folic acid needed to correct the blood conditions. B_{12} can also control or prevent the appearance of the symptoms of S.C.D., which are not affected by folic acid therapy.

Ungley[17] has given a very full account of the use of B_{12} in the control of pernicious anaemia. In general, 10 μg per week are often sufficient but he recommends 20 μg per week as a general practice, though much larger amounts may be needed on initiating treatment and in the control of S.C.D.

Assay of Vitamin B_{12}. Vitamin B_{12} may be assayed by a number of microbiological methods based on the observation that it is under certain conditions essential for the growth of some bacteria.[18-20] The vitamin may be estimated by normal procedures employing liquid media, while simple cup-plate methods similar to the Heatley penicillin assay technique have been described.[21, 22]

Standardized vitamin B_{12} concentrates of declared potency are now available and are doing much to simplify the control of pernicious anaemia.

MEGALOBLASTIC ANAEMIAS OTHER THAN PERNICIOUS ANAEMIA

The relation between folic acid and B_{12} in these conditions is still obscure and awaits further investigation.

Megaloblastic anaemia is associated with a large number of diseases. Apart from pernicious anaemia the more important are tropical and non-tropical sprue, coeliac disease, megaloblastic anaemias of infancy and pregnancy, nutritional megaloblastic anaemias, the megaloblastic anaemias following gastric resection or intestinal strictures, *Diphyllobothrium latum* infection and treatment with anti-folic acid drugs in the control of leukaemia.

Much of the work on these diseases is very difficult to interpret, probably because of difficulties in diagnosis and the different aetiology of conditions as they appear in different parts of the world. In America good responses in sprue and the anaemia of coeliac disease have been obtained with folic acid[23] and more recently with B_{12}.[24]

Nutritional macrocytic anaemias may be controlled with folic acid[25] and have also been found to respond to B_{12} both in America[26, 27] and in India[28] and also to folic acid.[25] It is probable that different workers in different parts of the world are not referring to the same conditions and in

different places the anaemia may be caused by deficiency in folic acid, in vitamin B_{12} or in both; the syndromes are often very complex, diet, malnutrition and its secondary absorption defects, sprue, hookworm and malarial infections, may all complicate it. Thus in England Ungley and Thompson [29] found the anaemia of pregnancy resistant to B_{12} therapy, but controlled by folic acid or yeast extracts, while Patel and Kocher [30] in India obtained good responses to B_{12}. Cameron *et al.*[31] observed that folic acid controls the anaemia following surgical formation of blind intestinal loops in the rat, while B_{12} is ineffective. Parenteral B_{12} controls the anaemia of *Diphyllobothrium latum* infection. The effects of B_{12} have been reviewed by Girdwood.[32]

In conclusion it may be stated that most of these anaemias will respond to folic acid, although in some instances B_{12} may also be required to obtain normal blood haemoglobin and red blood cells and in others B_{12} alone may be adequate.

ANIMAL REQUIREMENTS

Some years ago it was observed that experimental animals would not grow on diets of wholly vegetable origin even when supplemented with all the then known vitamins,[33] but adequate growth could be obtained if materials of animal origin, e.g. fish meal, meat meal or milk, were added to the diet. The substance or substances responsible for this effect came to be known as the Animal Protein Factor. Some difficulty was encountered in this work, because the activity could be passed on to the young animal through the placenta, the milk or the egg, so that in these studies it was often essential to use offspring from mothers maintained on the deficient diets.

Other observers had found that adequate growth could not be obtained with diets based on alcohol-extracted casein. This effect was attributed to the absence of factor X [34] or 'zoopherin' [35] found to be present in foods of animal origin. It was also reported that if certain substances, e.g. thyroxine [36] or lactose in large amounts,[37] were incorporated in the food, growth was depressed but could be restored if liver were added to the diet, though this beneficial effect could not be produced by any of the then known vitamins or other dietary components.

It has been found that all these conditions may be corrected by vitamin B_{12}, although in some instances [38] it will not completely correct the deficiency. It is now becoming clear that although B_{12} is the major component of the Animal Protein Factor, there is some other unknown factor also essential for adequate growth; thus chicks on certain wholly vegetable diets will not grow at maximal rates even if large amounts of B_{12} are added, but adequate growth may be obtained with certain fermentation products.[39] This second factor is not easy to investigate, because of the difficulty of obtaining deficient animals and of controlling the effects of the bacterial flora of the gut, which may produce or inactivate the growth factors being investigated.[40] However, it is clear that Vitamin B_{12} is essential for the growth of pigs and poultry and fortification with B_{12} may enable these animals to thrive on diets largely, if not wholly, of vegetable origin.

BIOCHEMICAL ROLE OF VITAMIN B_{12}

In man B_{12} deficiency, whether dietary (as in some nutritional macrocytic anaemias) or conditioned (as in pernicious anaemia), leads to a macrocytic anaemia and a megaloblastic bone marrow. In animals anaemia is not a typical symptom of B_{12} deficiency, although some alterations in the differential white cell count may occur.[41] It is not yet known what biochemical reaction is controlled by B_{12} in the blood-forming tissues. B_{12} deficiency in the rat has been shown to lead to an acute uraemia in the newly-born animals [42] and to decrease the hatchability of hen eggs.

ROLE IN NUCLEIC ACID METABOLISM

Thymidine and other deoxyribosides may replace B_{12} in the nutrition of B_{12}-dependent bacteria [43] but thymine, other pyrimidines or purines or deoxyribose will not. It is therefore supposed that B_{12} is an essential component of the enzyme system bringing about the combination between the sugar and the purines or pyrimidines. Friedkin *et al.*[44] have shown that deoxyribose phosphate may react with a purine to form the deoxyriboside. This observation suggests the attractive speculation that B_{12} may be essential for an enzyme system that phosphorylates deoxyribose, the sugar phosphate thus formed then reacting with the purines or pyrimidine bases to form the deoxyribosides, which in turn are used for the production of deoxyribonucleic acids. The role of B_{12} in nucleic acid metabolism is further illustrated by the observations of Roberts [45, 46] that this vitamin increases the rate of formation of deoxyribonucleic acid in *Lb. leichmannii* and the rate of phage (T4r) formation in *E coli*.

B_{12} is essential for the aerobic growth of *Lb. lactis*, but under certain anaerobic conditions [47] it may be dispensed with; B_{12} may therefore be a component of a redox system.

ROLE IN METABOLISM OF METHYL GROUPS

Methionine may replace B_{12} in the metabolism of *E. coli*.[48] Researches using the chick and rat have shown that a reciprocal relation exists between the B_{12} and methyl group (choline) requirements, B_{12} markedly reducing the choline requirements [49, 50] and preventing the fatty livers and haemorrhagic kidneys usually obtained on choline deficient diets. It has also been shown that B_{12} [51] prevents the development of fatty livers and hepatic fibrosis in rats fed on the high fat diet of Himsworth and Glynn. In chicks, B_{12}, folic acid and methyl groups are all essential components of the diet, but a decrease in one may be partially compensated by increasing the other two.[52] At the moment the conclusion may be drawn that B_{12} decreases the methyl group (choline and methionine) requirement of the rat and the chick, though it is not yet clear whether this effect is a direct one on the metabolic processes of the animal or whether it is mediated by the gut flora.

This work suggests that B_{12} might be of value in the

prevention or control of hepatic diseases of dietary origin so commonly observed in populations existing at low nutritional levels. So far no work on the use of B_{12} in the prevention and treatment of these conditions has yet been reported.

CONCLUSION

It may be said that B_{12} produces complete control of pernicious anaemia and is of importance in a number of other human macrocytic anaemias.

The vitamin is essential for pigs and chickens and may be of economic importance in allowing these animals to grow satisfactorily on readily available vegetable rations without the use of expensive animal protein supplements.

B_{12} has been shown to have beneficial effects in liver disorders produced in experimental animals by dietary methods. It is thus possible that it may have applications in the prevention or control of similar conditions in man.

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ABSTRACT

W. Brockbank. *The Treatment of Relapsing Malaria in General Practice.* Clinical Journal (1947): **76,** pp. 204-206.

On behalf of the general practitioner the author gives *inter alia* the following directions:

1. Quinine to be given in solution, 30 grains (= 2 gm.) daily for a week. (The question arises: why give such a large dose, which will cause chinchonism, to cure relapsing vivax malaria, when half that dose (1 gm.) will be quite sufficient. And why quinine in solution (with its barbaric taste), when easily dissolving tablets are manufactured by reliable firms?)
2. Pamaquin is most effectively given in combination with quinine. According to Brockbank 'pamaquin is mainly of use as a gametocide.' (As a matter of fact, the drug (and presumably also the newer substances of the group of 8-aminoquinolines, for instance pentaquin) kills the gametocytes of *Pl. falciparum,* but its main use lies in relapsing vivax malaria, to prevent relapses. However, a seven-day treatment (for instance with 1 gm. of quinine sulphate or hydrochloride and 60 mg. of pamaquin naphthoate daily) will not be sufficient; it should be continued for at least 10, at most 14 days.
3. Proguanil is best given in doses of from 250 mg. twice daily for 14 days, with a liberal quantity of fluid. The relapse rate is higher than if quinine and pamaquin are given in combination.
4. The author prefers mepacrine, sometimes preceded, however, by a preliminary two or three days of quinine, to ensure rapid control of the temperature.
5. Cerebral malaria should be treated with quinine intravenously, in a drip transfusion.

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VAN DIE REDAKSIE

RADIO-AKTIEWE JODIUM EN SKILDKLIERSIEKTES IN SUID-AFRIKA

Die Atoomtydperk in die genesende behandeling van die mens het in Suid-Afrika aangebreek. Pioniers-pogings in behandeling met radio-aktiewe isotope is in hierdie land gedoen deur Weinbren wat die eerste verhandeling oor die gebruik van radio-aktiewe fosfor in 1949 gepubliseer het.[1] 'n Jonger en selfs belangriker verslag deur dieselfde skrywer het onlangs verskyn onder die titel *Radio-Active Iodine in the Treatment of Thyroid Diseases: A Review of the Literature and Preliminary Report of Cases Treated.*[2] Hierdie artikel bevat die eerste menslike radio-outograwe wat in Suid-Afrika gepubliseer is.

Van 700 isotope wat so ver beskryf is, is slegs ongeveer 'n halfdosyn van praktiese mediese belang en hiervan is slegs twee van enige terapeutiese belang in Suid-Afrika, nl. radio-aktiewe fosfor (P^{32}) en radio-aktiewe jodium (I^{131}).

Verskeie nuwe en unieke probleme is geskep in verband met die vervoer van die isotope en die beskerming van die personeel wat by 'n program van behandeling betrokke is. Radio-aktiewe fosfor wat beta-strale afgee, veroorsaak nie dieselfde vervoer-moeilikhede as radio-aktiewe jodium nie, wat ook gamma-strale afgee.

Die probleem is gedeeltelik opgelos deur die skitterende wenk van dr. Halliday (op die personeel van die Wetenskaplike en Nywerheidnavorsingsraad, Pretoria), dat radio-aktiewe isotope in die vlerkpunte van vliegtuie vervoer word en afstand in plaas van lood gebruik word vir die beskerming van personeel en goedere wat vir uitstraling vatbaar is.

Die ander bevredigende gevolg van hierdie metode van vervoer is die ontsaglike vermindering in die koste van die isotope. Dit is vandag moontlik om in hierdie land radio-aktiewe jodium vir terapeutiese doeleindes as 'n roetine-metode van behandeling te gebruik.

Radio-aktiewe jodium het 'n diagnose- sowel as 'n genesingsfunksie. Klein (speur-) dosisse word in die

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EDITORIAL

RADIO-ACTIVE IODINE AND THYROID DISEASES IN SOUTH AFRICA

The Atomic Age of human therapy has dawned in South Africa. The pioneering therapeutic efforts with radio-active isotopes in this country were instituted by Weinbren, who published his first paper on the use of radio-active phosphorus in 1949[1]. A more recent and even more important report by the same author has recently appeared entitled *Radio-Active Iodine in the Treatment of Thyroid Diseases: A Review of the Literature and Preliminary Report of Cases Treated*[2]. This article includes the first human radio-autographs to be published in South Africa.

Of the 700 isotopes so far described, only some half a dozen are of practical medical importance and of these only two are of any therapeutic importance in South Africa, viz. radio-active phosphorus (P^{32}) and radio-active iodine (I^{131}).

Several new and unique problems affecting the transport of the isotopes and the protection of the personnel involved in a therapeutic programme have been created. Radio-active phosphorus, which gives off beta rays, does not offer the same transport difficulties as radio-active iodine, which gives off gamma rays as well.

The problem was partly solved by the brilliant suggestion of Dr. Halliday (on the staff of the Council for Scientific and Industrial Research, Pretoria), that the radio-active isotopes be transported in the wing-tips of aeroplanes, using distance instead of lead as a protection for personnel and goods susceptible to radiation.

The other satisfactory consequence of this method of transport has been the immense reduction in the expense of the isotopes. To-day the use of radio-active iodine is possible for therapeutic purposes as a routine method of treatment in this country.

Radio-active iodine has a diagnostic as well as a therapeutic function. In the form of a diagnostic

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vorm van 'n diagnosetegniek gebruik. Met behoorlike geriewe en bedrewe fisici is die gebruik van radio-aktiewe jodium as 'n speurdosis 'n noukeuriger metode om skildklierfunksie te bepaal as die Basale Metaboliese Snelheid of die berekening van die proteïengebonde bloedjodium.[3] Die speurtoets met radio-aktiewe jodium sal dus waarskynlik met verloop van tyd ander toetse vervang, veral by pasiënte by wie dit moeilik is om die B.M.S. te meet, d.w.s. gevalle van hartvaatsiekte met wisselende grade van verswakking, asmalyers, psigote en gevalle met leukemie en Hodgkinsiekte.

Die speurtoets wend die wyd erkende fisiologiese feit aan dat die skildklierweefsel 'n opvallende spesifieke affiniteit vir jodium het. Die radio-aktiewe jodium word dus deur die skildklier opgeneem en die hoeveelheid wat in die skildklier aanwesig is asook die hoeveelheid wat in die uriene afgewerp word, kan baie eenvoudig deur Geiger-Müllermeters gemeet word.

'n Groter hoeveelheid radio-aktiewe jodium is vir genesende behandeling nodig. Besonder geskik vir kwale van die skildklier, is hierdie middel vir goed- sowel as kwaadaardige ongesteldhede van die skildklier gebruik.

Ongelukkig het radio-aktiewe jodium by die behandeling van skildklierkanker uiters teleurstellend geblyk. Alhoewel ongeveer 15% skildklierkankers verskillende hoeveelhede radio-aktiewe jodium opneem, reageer slegs 5% bevredigend. Die radio-aktiewe jodium se grootste waarde lê egter by die ontdekking van vroeë sekondêre neerslae en die behandeling van hierdie sekondêre neerslae wat die radio-aktiewe jodium opneem en die primêre gewas aan die snykundige vir verwydering oorlaat.

Gevalle met talryke neerslae in die longe het na die toediening van radio-aktiewe jodium gesond geword. Weinbren het egter daarop gewys dat hierdie gevalle nie eers met X-straling behandel is nie en sy ondervinding dui daarop dat X-straling eers probeer moet word ten einde die toediening van die uiters groot hoeveelhede radio-aktiewe jodium te voorkom wat nodig is vir die behandeling van sekondêre neerslae. (Die groot dosisse wat nodig is vir die behandeling van sekondêre neerslae kan bloedarmoede, leukopenie, trombositopenie en amenoree veroorsaak.)

Die vernaamste en bevredigendste gebruik van radio-aktiewe jodium is egter by die behandeling van oormatige skildklierwerking. Alhoewel die behandelingstegniek eenvoudig is, is die berekening van die millicurie-dosis moeilik. Radio-aktiewe jodium word deur die mond aan die pasiënt toegedien en daar is baie min sydelingse uitwerkinge, indien enige. Bestralingsiekte, lugpypontsteking en aptytverlies in ligte graad is berig, maar Weinbren het nie hierdie verwikkelinge by sy gevalle teengekom nie. Tiorasiel moet gestaak word vier dae voor die radio-aktiewe jodium toegedien word, en geen jodium moet vir minstens 'n maand voor die tyd toegedien word nie.

3. Jaffe, H. L. en Ottoman, R. E. (1950): J. Amer. Med. Assoc., **143**, 515.

technique, minute (tracer) doses are used. Given proper facilities and skilled physicists, radio-active iodine, as a tracer dose, is a more accurate method of determining thyroid function than the B.M.R. or the estimation of the protein-bound blood iodine[3]. The radio-active iodine tracer test is, therefore, likely to replace other tests in the course of time, particularly in patients in whom it is difficult to measure the B.M.R., e.g. cases of cardio-vascular disease with varying degrees of failure, asthmatics, psychotics and cases with leukaemia and Hodgkin's disease.

The tracer test makes use of the well-established physiological fact that the thyroid tissue has a specially marked affinity for iodine. The radio-active iodine is therefore taken up by the thyroid gland and the amount present in the thyroid as well as the amount excreted in the urine can be measured very simply with Geiger-Müller counters.

In the therapeutic sphere, much larger quantities of radio-active iodine must be used. Specially suited to disorders of the thyroid gland, this new agent has been tried in benign as well as malignant disorders of the thyroid.

Unfortunately the value of radio-active iodine in the treatment of thyroid cancer has proved very disappointing. Although some 15% of thyroid cancers take up various quantities of radio-active iodine, only some 5% respond satisfactorily. The radio-active iodine, however, has its main value in the detection of early secondary deposits and in the treatment of these secondary deposits, which take up the radio-active iodine in turn, leaving the surgeon to remove the primary growth.

Cases with numerous pulmonary secondary deposits have cleared up following radio-active iodine. Weinbren, however, has pointed out that these cases have not first been treated with X-radiation and his experience suggests that X-radiation should be attempted first in order to avoid giving the very large quantities of radio-active iodine required for the treatment of secondary deposits. (The large doses necessary for the treatment of secondary deposits may cause anaemia, leucopaenia, thrombocytopaenia and amenorrhoea).

The main and most satisfactory use of radio-active iodine, however, is in the treatment of hyperthyroidism. Although the technique of treatment is simple, the estimation of the millicurie-dose is difficult. Radio-active iodine is given to the patient by mouth and there are very few, if any, side-effects. Radiation sickness, tracheitis and anorexia of a mild degree have been reported, but Weinbren did not encounter these complications in his cases. Thiouracil must be stopped four days before the radio-active iodine is given and there should be no iodine medication for at least a month beforehand.

3. Jaffe, H. L. and Ottoman, R. E. (1950): J. Amer. Med. Assoc., **143**, 515.

Daar is verskil van mening oor die wyse waarop die terapeutiese dosis toegedien moet word. Sommige terapeute verkies om 'n enkele genesende dosis toe te dien en loop die risiko om skildkliergebrek of miksedeem by 'n sekere persentasie gevalle te veroorsaak. Ander verkies verdeelde dosisse en herhaal die behandeling na 'n pouse van drie of vier maande. Aanspraak word daarop gemaak dat hierdie tegniek wat deur Weinbren gevolg is, veiliger is en minder waarskynlik skildkliergebrek sal veroorsaak. Dit is egter nie moontlik om met sekerheid te voorspel watter dosis in enige afsonderlike geval 'n gebalanseerde skildklierwerking of skildkliergebrek sal veroorsaak nie. Aanspraak word daarop gemaak dat die uitslae buitengewoon goed is.[4]

Die behandelingsaanwysings is duidelik vasgestel:

1. *Definitiewe oormatige skildklierwerking,* wanneer die skildkliervergroting nie veel meer as drie tot vier maal sy normale grootte is nie.

2. *Herhaalde oormatige skildklierwerking nadat skildklier een of meer keer verwyder is.* Die uitslae in hierdie groep is besonder bevredigend en Weinbren wys daarop dat goeie uitslae in hierdie gevalle baie min radio-aktiewe jodium vereis.

Die teenaanwysings is netso duidelik vasgestel:

1. *Baie groot skildkliere met of sonder druksimptome* is nie vir behandeling geskik nie.

2. *Die groot knopperige soort skildkliergeswel* het in die geval van alle navorsers nie goed gereageer nie.

3. *Gevalle van strawwe skildkliervergiftiging.* Dié vereis toereikende voorbereiding met tiorasiel voordat radio-aktiewe jodium toegedien word.

4. *Swangerskap* is nog 'n teenaanwysing.

5. Daar is te kenne gegee dat die uitwerking van bestraling na baie jare *neoplastiese verandering* te weeg kan bring. Tot dusver is geen geval van ontwikkeling van kwaadaardige skildklier aangemeld nie, òf na behandeling met die isotope òf as gevolg van bestraling aan die buitekant. Baie fisici reken dat die moontlikheid van kwaadaardige verandering uiters skraal is maar om heeltemal veilig te wees is aan die hand gedoen dat die behandelingsmetode nie in die geval van pasiënte onder 20 jaar gevolg moet word nie. Doniach het egter met radio-aktiewe jodium adenomata in die skildklier van die rot te weeg gebring.[5] Hierdie waarneming dui sekerlik op die behoefte om versigtig te wees. Daar is nietemin kinders wat met sukses behandel is.

DIE PROBLEME WAT VOORTVLOEI UIT DIE GEBRUIK VAN RADIO-AKTIEWE JODIUM

Weens die hoeveelheid radio-aktiewe jodium wat vir die behandeling van kwaadaardige skildkliere nodig is, ontstaan die uiters belangrike probleem van die beskerming van die personeel wat die radio-aktiewe jodium toedien.

Tweedens is daar die probleem van die samestelling van die personeel. Moet die behandeling aan die

4. Gordon, S. en Albright, E. S. (1950): J. Amer. Med. Assoc., **143,** 1129.
5. Doniach, I. (1950): *Aangehaal deur* Weinbren, M. (1950): S. Af. J. Clin. Sci., **1,** 283.

Opinion is divided about the manner of giving the therapeutic dose. Some therapists prefer to give a single curative dose and run the risk of producing hypothyroidism or myxoedema in a certain percentage of cases. Others prefer split doses, repeating the treatment after an interval of three or four months. This technique, adopted by Weinbren, is claimed to be safer and less likely to produce hypothyroidism. It is not possible, however, to predict with certainty what dose will, in any one case, produce a euthyroid or a hypothyroid state. The results are claimed to be extraordinarily good[4].

The indications for treatment are quite definite:

1. *Definite hyperthyroidism,* when the thyroid enlargement is not much more than three to four times normal.

2. *Recurrent hyperthyroidism after one or more thyroidectomies.* The results in this group are particularly gratifying and Weinbren points out that good results in these cases require very little radio-active iodine.

The contra-indications are equally definite:

1. *Very large thyroids with or without pressure symptoms* are not suitable for treatment.

2. *The large nodular type of goitre* has not responded well in the hands of all investigators.

3. *Cases of very severe thyrotoxicosis.* These need adequate preparation with thiouracil before the radio-active iodine is given.

4. *Pregnancy* is another contra-indication.

5. It has been suggested that the effect of the radiation may produce *neoplastic changes* many years later. So far no case of the development of a malignant thyroid has been reported, either following treatment with the isotope or as a result of external radiation. Many physicists regard the possibility of malignant changes as very small, but to be on the safe side, it has been suggested that this method of treatment should not be used on patients under 20 years of age. Doniach, however, has produced adenomata in the rat thyroid with radio-active iodine[5]. This observation certainly suggests the need to exercise great caution. There are children, nevertheless, who have been treated successfully.

THE PROBLEMS PRODUCED BY THE USE OF RADIO-ACTIVE IODINE

Because of the large quantity of radio-active iodine required for treating malignant thyroids, there is the very important problem of the protection of the personnel administering the radio-active iodine.

Secondly there is the problem of who should comprise the personnel. Should the treatment be left to a

4. Gordon, S. and Albright, E. S. (1950): J. Amer. Med. Assoc., **143,** 1129.
5. Doniach, I. (1950): *Quoted by* Weinbren, M. (1950): S. Af. J. Clin. Sci., **1,** 283.

geneesheer bygestaan deur 'n fisikus oorgelaat word, of moet die fisikus 'n radioterapis bystaan?

In Suid-Afrika is daar baie min geneeshere of fisici wat opgelei is om die gevare en die tegniese probleme te begryp wat met bestralingsterapie van enige aard in verband staan. Daarbenewens is dit te betwyfel of, afgesien van 'n paar lede van die personeel van die Wetenskaplike en Nywerheidnavorsingsraad en die Universiteite daar 'n toereikende aantal fisici is wat 'n spesiale studie gemaak het van die probleme wat by bestralingsterapie betrokke is. Die enigste mense wat die probleem insien, afgesien van die opgeleide fisici, is die radioloë. Dit lyk klaarblyklik dat die beste uitslae verkry sal word van 'n span wat bestaan uit 'n geneesheer, 'n fisikus, 'n patoloog en 'n radioloog.

Wat met die ontlasting gedoen moet word, is 'n daadwerklike probleem en dit het die owerhede in Groot-Brittanje sowel as die Verenigde State hoofbrekens besorg. Die moeilikheid word geskep deur die uriene van die behandelde pasiënte aangesien dit weens sy inhoud van radio-aktiewe jodium spesiaal geberg moet word voordat dit weggeruim word. In Groot-Brittanje byvoorbeeld word elke keer 'n beperkte hoeveelheid van die radio-aktiewe uriene binne 'n vasgestelde tydperk in riviere soos die Teems en op uitloopplekke van isoleringstelsels vrygelaat.

'n Distribusieprogram is netso belangrik. In Pretoria en Johannesburg het behandeling met radio-aktiewe jodium reeds op aansienlike skaal plaasgevind; maar daar bestaan werklik geen rede waarom hierdie behandeling nie in Kaapstad, Durban, Port Elizabeth, ens., kan plaasvind nie. Die enigste moeilikheid is die gebrek aan opgeleide fisici en dit is 'n beswaar wat in die belang van die publiek haas nie in die Atoomtydperk geduld kan word nie.

physician with the help of a physicist, or should the physicist assist a radiotherapist?

In South Africa there are very few physicians or physicists trained to appreciate the dangers and the technical problems associated with radiation therapy of any description. Moreover, it is doubtful whether, apart from a few members on the staff of the Council for Scientific and Industrial Research and the Universities, there are adequate numbers of physicists who have made a special study of the problems involved in radiation therapy. The only people who appreciate the problem, apart from specially trained physicists, are the radiologists. It seems obvious that the best results would be obtained from a team consisting of a physician, a physicist, a pathologist and a radiologist.

The problem of the disposal of excreta is a very real one and has exercised the minds of the authorities both in Great Britain and the United States. The difficulty is provided by the urine of the treated patient as it must be specially stored before disposal because of its radio-active iodine content. In Great Britain, e.g. the radio-active urine is discharged, a limited amount at and within a stipulated time, into rivers such as the Thames or on to sewerage farms.

Equally important is a programme of distribution. Treatment with radio-active iodine is already being carried out on a considerable scale in Johannesburg and Pretoria; but there is really no reason why this treatment should not be carried out in Cape Town, Durban, Port Elizabeth, etc. The only difficulty is the lack of trained physicists and this is hardly an objection which can be countenanced, in the public interest, in the Atomic Age.

PULMONARY MANIFESTATIONS AND DEATHS DUE TO THE INGESTION OF PETROLEUM PRODUCTS

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Poisoning due to swallowing of petroleum products, e.g. kerosene (called paraffin in South Africa) and benzine are as common in the urban Bantu child as they are in the urban population of the United States (Chicago, etc.).[1] These cases represent 1% of our in-patient admissions each year. In two years we have admitted 29 cases of petroleum products poisoning; 25 cases were kerosene poisoning and four were benzine poisoning. There was one death in each group.

Deaths were stated to be uncommon. Detailed reports of the autopsy were supplied by the Government Mortuary. In this paper the cases will be divided into three groups:

1. Cases with rapid recovery.
2. Cases in which the symptoms were severe and recovery rate prolonged.
3. Cases which showed severe toxaemia and neurological signs. Included in this group are two deaths.

No attempt will be made to explain the cause of death of the patient. It is assumed that the intoxication is due to the aspiration of kerosene.[2] The pneumonic changes can readily be seen in the X-ray findings; these are very often in marked clinical contrast to the seeming well-being of the patient. In fact, it was difficult to persuade Bantu parents that their children were ill enough to warrant hospitalization.

Group 1. There were 11 cases in this group—in which recovery was rapid. In most of the cases the definite amount of the ingested material could not be ascertained. These patients all recovered, they had few signs and symptoms (Table 1). In four cases there were no signs of chest involvement. This was confirmed by X-ray findings. There was only one case that was

TABLE 1

No.	Age (Months)	Sex	Poison	Approximate Amount (oz.)	Hours before Admission	Hospital Stay (Days)	History	Examination	X-ray	Treatment	Remarks
1	21	M	Kerosene	?	?	2	Unimportant	No physical signs	Negative findings	Sulphadiazine	Cured
2	13	M	,,	?	6	*	Unimportant	Slightly ill. Rhonchi on both sides of chest. Temperature 102° F. returned to normal	Slight bilateral bronchopneumonic changes	Sulphadiazine	Cured
3	17	M	,,	?	6	3	Unimportant	Not ill. Chest clear. Temperature 102° F., normal next day	Negative findings	Sulphadiazine	Cured
4	19	M	,,	?	1	2	Coughing—vomiting	No physical signs	Negative findings	Sulphadiazine	Cured
5	24	M	,,	?	½	*	Unimportant	No physical signs	Pneumonitis left base	Sulphadiazine	Improved
6	12	F	,,	?	2	*	Coughing—vomiting	Slightly ill, crepitations right base	Pneumonitis right base	Sulphadiazine	No change
7	22	M	,,	1	4	5	Coughing	Eyes suffused. Pulse 160 per minute. No physical signs	Negative findings	Sulphadiazine	Cured
8	21	F	,,	2	2	2	Unimportant	Pulse 140. ?Triple rhythm at apex	Slight broncho-pneumonic changes	Hospital	Cured
9	24	M	,,	½	2	1	Coughing	No physical signs	Bilateral broncho-pneumonia	Penicillin	Cured
10	72	M	Benzine	?	1	2	Vomiting—drowsy	No physical signs	Not done	Sulphadiazine	Cured
11	16	M	Kerosene	3	1	3	Unimportant	No physical signs	Increased shadows left upper zone	Hospital	Cured

* Patient taken out of Hospital against medical advice.

TABLE 2

No.	Age (Months)	Sex	Poison	Approximate Amount (oz.)	Hours before Admission	Hospital Stay (Days)	History	Examination	X-ray	Treatment	Remarks
12	14	M	Kerosene	?	1	6	Coughing, blood-stained vomit	No physical signs	Negative findings	Hospital	Cured
13	13	M	,,	½	3	*	Coughing—vomiting	Ill. Rhonchi both lung fields. Pulse 180. Temperature 103° F.	Pneumonitis left upper zone	Sulphadiazine	No change
14	21	M	,,	?	?	7	Unimportant	Ill. No physical signs	Negative findings	Sulphadiazine	Cured
15	12	F	,,	1	?	?	Unimportant	Ill. No physical signs	Bronchopneumonia both bases and base of right upper lobe	Sulphadiazine	Cured
16	19	M	,,	3	5	5*	Unimportant	Dyspnoeic. Rhonchi both lungs. Temperature 104° F., normal in five days. Pulse 106 per minute	Bilateral broncho-pneumonia, right paratracheal glands enlarged. ?Tuberculous	Sulphadiazine Penicillin & Streptomycin	Improved Patch test*
17	18	F	,,	½	1	6	Coughing	Ill. Pulse 150 per minute	Broncho-pneumonia	Oxygen Sulphadiazine Penicillin	Cured
18	15	M	,,	5	6	9	Unimportant	Dyspnoea and tachy-cardia (160). Impaired percussion, right base	Bilateral broncho-pneumonia with shadowing at right base	Sulphadiazine	Cured
19	18	M	,,	2	1	3	Coughing	Dyspnoea. Cyanosis. Pulse 150, crepitations both bases. Hepato-splenomegaly	Bilateral broncho-pneumonia	Suction Oxygen Penicillin	Cured
20	17	F	,,	2	6	5	Coughing	Dyspnoea. Eyes suf-fused. Prolonged tachy-cardia	Atelectasis right middle lobe	Sulphadiazine	Cured

* Patient taken out of Hospital against medical advice.

TABLE 3

No.	Age (Months)	Sex	Poison	Approximate Amount (oz.)	Hours before Admission	Hospital Stay (Days)	History	Examination	X-ray	Treatment	Remarks
21	16	M	Kerosene	?	4	*	Vomited	Drowsy. Temperature 103° F.	Not done	Hospital	No change
22	20	M	„	3	96	5	Vomited, diarrhoea convulsions	Eyes suffused. Dullness and crepitations right side. Pulse, 140. Temperature 104° F.	Slight broncho-pneumonic changes at right base	Sulphadiazine Benadryl	Cured
23	13	F	„	2	1	2	Vomited. Fainted	Very ill. Stuporose, convulsions; Pulse 160	Shadows right side	Oxygen Sulphadiazine Penicillin	Died
24	16	F	Benzine	?	6	5	Blood-stained vomit	Ill. Pulse 160, coma	Patchy pneumonitis right base	Lavage Analeptics Penicillin	Cured
25	14	F	Kerosene	?	2	4	Coughing, vomiting	Dyspnoeic Drowsy. Pulse 160. Temperature 104° F.	Pneumonitis right base	Sulphadiazine	Cured
26	20	F	„	1	1	4	Coughing	Drowsy, pulse 140. Temperature 101° F.	Pneumonitis left base	Sulphadiazine	No follow up
27	24	M	Benzine	?	2	1*	Blood-stained vomit	Ill. Pulse 130	Pneumonitis left base	Hospital	No follow up
28	17	F	Kerosene	?	4	10	Coughing, vomiting, epitaxis	Stuporose. Cyanosed. Dyspnoeic. Fast thready pulse. Temperature 102° F. Respiration 80. No signs in chest	Mottling both cardiophrenic angles	Oxygen Penicillin Analeptics	Cured
29	17	F	Benzine	6	2 hour	½	Coughing, vomiting	Very ill. Cyanosed. Stuporose, very moist chest	Not done	Lavage Oxygen Intravenous drip Analeptics Antibiotics	Died

* Patient taken out of Hospital against medical advice.

drowsy and had a tachycardia, six cases showed changes in the lungs, and three of these showed physical signs of lung changes. The average hospital stay in this group was from two to three days.

Group 2. This group included nine patients. They showed more extensive chest involvement than group one. All nine cases were X-rayed; in two cases X-ray findings were negative. The remaining seven cases had definite X-ray involvement of the chest. The average hospital stay in this group was five to six days.

Group 3. There were nine patients in this group. These patients showed signs of severe toxaemia and convulsions were not an unusual feature. Drowsiness, dyspnoea, cyanosis and tachycardia were the common features of this group; they were extremely ill and gave rise to apprehension on our part. These patients vomited blood-stained fluid. It was in this group that we had two deaths. The average hospital stay in this group was also six days.

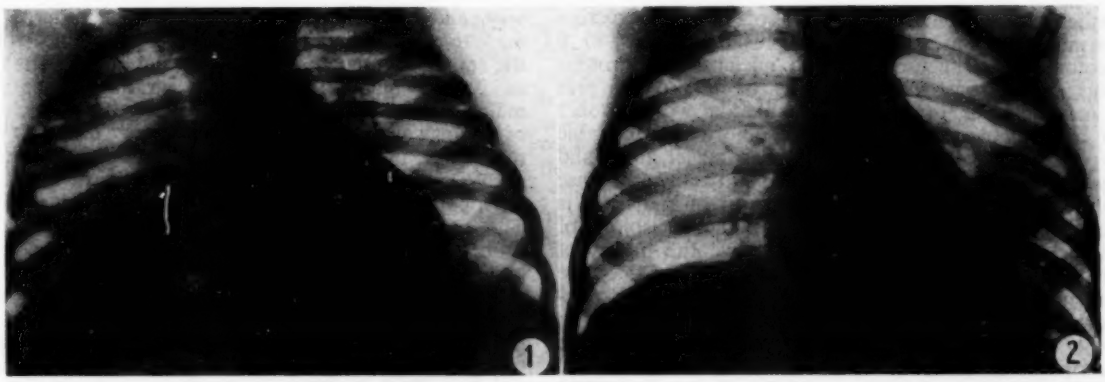
Absorption of kerosene may be the causes of these toxic changes mentioned above. Steiner [1] remarks: 'Clinically it appears that absorption from the stomach has enough potentiality for pathological effect to warrant the prompt removal by lavage'.

Fatal Cases. These were:

1. *Death due to Kerosene*: The patient was a 13-month-old Bantu female child who drank 2 oz. of kerosene about an hour before admission. She vomited and fainted. Examina- showed a crying, irritable, drowsy child. The temperature was normal, the pulse rate was 120 per minute and respirations were 30 per minute. There were no signs of chest involvement. Later in the afternoon her condition gave rise to anxiety, she was placed in an oxygen tent, lobeline, sulphadiazine and penicillin were administered. At this time there was a leucocytosis of 11,000 per c.mm. She seemed to rally and at 3.30 a.m. on 13 January 1949 she was fully conscious. Three hours later, however, she was stuporose. The pulse rate was 160 per minute and the patient commenced Cheyne-Stokes respiration. There were rhonchi in both lungs. The pupils reacted sluggishly to light, all the limbs were hypertonic and there was a positive Babinski response on the right side. A bed-side X-ray showed shadows on the right side. That afternoon the patient had generalized convulsions. These began with carpo-pedal spasm. The patient was placed on intravenous therapy: dextrose, luminal and calcium gluconate were given via the drip. The patient continued having convulsions, more marked on the right side. Death occurred two days after admission.

Investigations: Lumbar puncture was performed. The fluid was clear, there were no cells or organisms. Protein was 15 mg. per 100 c.c., the sugar was also 15 mg. per 100 c.c. The white cell count was 17,500 per c.mm. with neutrophils. 79.5% and lymphocytes 18%; the red blood count was 4,050,000 per c.mm. The Wassermann reaction was negative; blood protein, 5.1%, and the blood sugar was 105 mg. per 100 c.c. Blood calcium, 13.6 mg. per 100 c.c., alkaline phosphatase, 22.5 King-Armstrong units; urine: sugar +, acetone ++.

At autopsy the brain was found to be congested, but there was no smell of kerosene. The right side of the heart was distended and the heart muscle pale. The lungs were con-



gested. Thick muco-pus was present at the lower end of the trachea, and in the bronchi and bronchioles. There was no smell of kerosene in the stomach. The mucosa of the small bowel was atrophied, and greenish fluid faeces were present throughout the whole of the small gut. There was a fatty degeneration of the liver. Spleen and both kidneys were congested.

2. *Death due to Benzine*: A 17-month-old Bantu female child was admitted at 9.30 a.m. on 8 December 1949. She had consumed 6 oz. of benzine two hours before admission. On examination she was stuporose and cyanosed. Laryngo-tracheal aspiration was done, she was given Eucortone and lobeline. She was placed in an oxygen tent. Suction was applied with a stomach tube. After this vomiting occurred and the vomitus had a strong benzine odour. Despite intravenous atropine and intracardiac adrenalin she died half-an-hour after admission.

At autopsy, the brain was found to be congested and oedematous. The right side of the heart was distended and the heart muscle pale. There was a large thymus, and large lingual tonsils. There was a haemorrhagic, confluent bronchopneumonia throughout both lungs. The gut was normal, but the mesenteric glands were hypertrophied. The liver was pale. The spleen was large and pale, with a marked increase of lymphoid tissue.

Typical X-ray films of kerosene poisoning (Fig. 1, Case 18 of Group 2) and benzine poisoning (Fig. 2, Case 27 of Group 3) are included.

SUMMARY AND CONCLUSIONS

With the exception of one child of six years, 28 of the 29 cases were between one and two years of age. There were two deaths in this series. Most of the cases had a leucocytic process. The erythrocyte sedimentation rate was only slightly increased. In three cases prothrombin estimations were done, and were normal. An outstanding feature in all cases was tachycardia. The common rate was from 140-160 a minute, and tended to remain elevated during and even upon discharge from hospital.

Lung changes occurred in 77% of our patients. Despite the apparent well-being of the patients X-ray changes showing pneumonitis were found in many patients. This held true of the one case of benzine poisoning that recovered. There is no apparent relationship between the toxic manifestations and the amount swallowed.

Changes in benzine poisoning are similar to those of kerosene poisoning.

In the group that consumed kerosene, the death rate was 4%. In the four cases of benzine poisoning, the death rate was 25%.

We wish to thank Prof. Macintosh of the Government Laboratory for the autopsy reports.

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RADIO-ISOTOPES IN MEDICINE

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The name *isotope* was first coined when it was discovered that there could be two or more elements behaving chemically in exactly the same way, but differing in atomic weight. The chemical behaviour of an element is determined by the arrangement and number of the electrons outside the nucleus. This number, called the *atomic number*, is exactly the same as that of the protons inside the nucleus, the negative charge on the almost weightless extra-nucleur electrons balancing the positive charge on the nuclear protons. The nucleus also contains neutral particles, or neutrons, and the *atomic weight* is given by the total of neutrons and protons. Thus we have one type of carbon, $6C^{12}$, which has 6 extranuclear electrons, and 6 protons plus 6 neutrons in the nucleus. This is the commonest form of the carbon atom; but an isotope of carbon, $6C^{13}$, has 7 neutrons plus 6 protons in the nucleus.

Most common elements have one or more isotopes which are stable, i.e. the nucleus remains unchanged through the ages. The requirements for stability are

rather strict. The energy laws of nuclear structure permit a nucleus of 6 protons plus 6 neutrons, or 6 protons plus 7 neutrons, but a nucleus of 6 protons plus 5 neutrons ($6C^{11}$) or one of 6 protons plus 8 neutrons ($6C^{14}$) would be unstable and would sooner or later spontaneously change in some way to a stable type. A few elements with unstable nuclei are found in nature, and these are called radio-active, because when the nucleus changes some form of radiation is emitted. A naturally occurring radio-active isotope of biological interest is K^{40}. If we have the means of changing a nucleus, e.g. by adding a neutron to it, we can make it unstable and it will sooner or later spontaneously change into a stable form and in so doing emit radiation; we have then made a radio-active isotope of the element we started with.

Keeping to carbon as an example: if we take a $6C^{13}$ atom (stable isotope of carbon) and cause a neutron to be captured by the nucleus, we now have $6C^{14}$, with its nucleus of 6 protons and 8 neutrons. This instability is adjusted by the spontaneous conversion of a neutron into a proton, giving a nucleus of 7 protons, 7 neutrons, and therefore when the atom becomes neutral it has atomic number 7, atomic weight 14—i.e. we now have a nitrogen atom. Note that the atomic weight has not changed. For a neutron to be converted into a proton, it must emit a unit negative charge, thereby acquiring unit positive charge. This emitted charge is in the form of the electron, or beta ray, when it originates in this way, and carbon 14 is thus a beta-ray emitter. The nuclear re-adjustment which takes place often involves the emission of gamma rays, which are of the same type as X-rays but much more penetrating. The vast majority of radio-isotopes, particularly those which are of biological importance, are emitters either of beta rays alone, or of beta rays and gamma rays together.

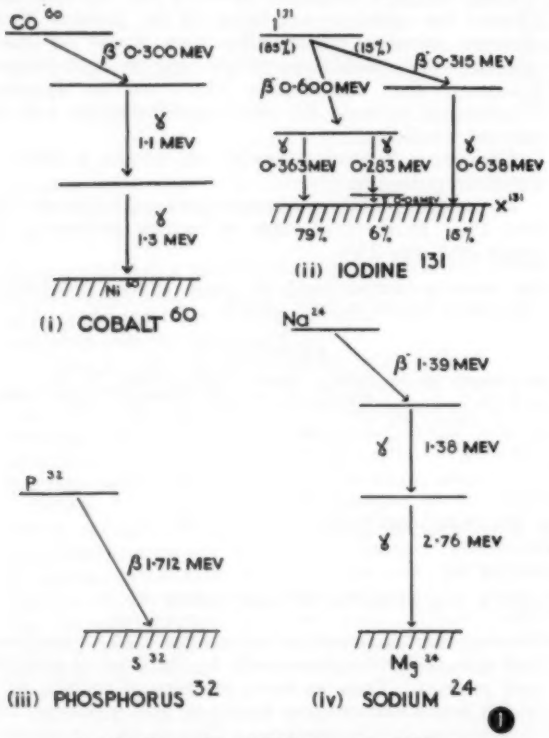


Fig. 1. Examples of Disintegration Schemes.

Every type of unstable nucleus has its own characteristic radiation and its own measure of instability. The more unstable a nucleus is, the greater is its probability of disintegrating within a short time. In any radio-element we find that the fraction of the number of atoms disintegrating within a certain time is characteristic, and a convenient concept is that of the half-life, i.e. the time after which the number of atoms surviving will be just half of the number originally present. This half-life varies from a fraction of a second to millions of years. For example Na^{24} has a half-life of 14.8 hours, while C^{14} has a half-life of over 5,000 years. It must be remembered that in every half-life the number of radio-active atoms is halved, so that after 6 half-lives, for example, we have left $1/2^6$ or 0.016 of the original amount.

TABLE OF ENERGIES AND HALF-LIVES

The following are some of the radio-elements of most interest in biology:

Radio-isotope	*Half-life*	*Maximum Beta-ray Energy*	*Gamma-ray Energy*
C^{14}	>5,000 years.	0·156 Mev.	——
Na^{24}	14·8 hours.	1·39 Mev.	1·38, 2·76 Mev.
P^{32}	14·3 days.	1·70 Mev.	——
Ca^{45}	152 days.	0·25 Mev.	——
Fe^{55}	4 years.	——	(X-rays) 5·9 Kev.
Fe^{59}	47 days.	0·46 Mev.	1·10, 1·30 Mev.
Co^{60}	5·3 years.	0·31 Mev.	1·10, 1·30 Mev.
I^{131}	8·0 days.	0·69 Mev.	0·367, 0·080, 0·65 Mev.
Au^{198}	2·7 days.	0·98 Mev.	0·41, 0·16, 0·21 Mev.

The fact that radio-isotopes give off radiation makes for delicacy of detection which cannot be approached by any chemical means. With suitable but quite ordinary apparatus one can, e.g. detect as little as $5X10^{-17}$ gm. of P^{32}, or a total of only 1 million atoms. In addition to being able to detect infinitesimal quantities of an element, we are able to label many elements when and where we wish, and can trace the course of the labelled element. No chemical procedure can distinguish between sodium which has been present in an organism for some time, and that which has been injected at a particular moment. But if the injected sodium is labelled with radio-sodium atoms, we can follow its course by measuring the radio-activity of any sample in which we are interested.

A second factor of great interest in medicine is the effect on living tissue of the radiations from radio-elements. These have the same sort of effects as X-rays, or the gamma rays from radium, and can in certain circumstances be used therapeutically, or they can be used for investigating the biological effects of such radiations.

In general we can divide into two major groups the

vast number of uses to which radio-isotopes are put: tracer uses and therapeutic uses. They are distinguished by the different order of magnitude of the amounts of activity used. In tracer techniques minute quantities are administered, far less than for any biological effects of the radiation to be significant or perceptible. Measurement techniques are of great importance and are often not as simple as the literature might indicate. The apparatus most commonly met with is based on the Geiger counter as the detecting agent, and this may have one of many forms, depending on the nature of the investigation. A useful type for body or other

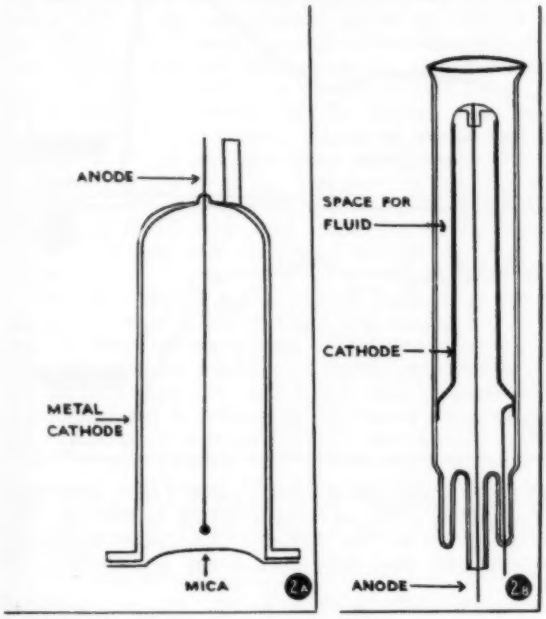


Fig. 2. Some types of Geiger-Müller counter.

fluids is that developed by Veall.[1] In this counter a sample of the fluid is poured into a glass skirt surrounding the actual counter. Counters of this type are being made by a commercial firm in England. The Geiger counter must be fitted inside a lead 'castle' in order to shield it from cosmic and other external radiation. The impulses from the Geiger counter are fed (often through an amplifier) to a scaling unit. There is a large variety of makes of all the components on the market. A modest set of equipment for doing tracer work should cost about £350, but it will be realized that the instruments to be chosen depend on the investigation being undertaken.

It is also important to realize that the ideal radio-isotope cannot always be found for helping in the solution of a special problem. The half-life of the radio-element and the energy and type of its radiations impose restrictions on, and sometimes present very great difficulty to, those who wish to use it with human beings. For *in vivo* experiments we must in general employ a radio-element which emits gamma rays; C^{14}, Ca^{45} and P^{32}, e.g. do not. They are pure beta-rayers and beta rays are absorbed by a millimetre or two of tissue. P^{32} does give off very energetic beta rays and can be used in investigations over the surface of the body, but Ca^{45} gives off very soft, easily absorbed beta rays and demands rather special types of Geiger counter if it is to be measured efficiently. Then, again, the half-life of a radio-element is a very important consideration. Probably no one would wish to use C^{14} in an investigation involving human beings, as its half-life is over 5,000 years and one would not wish to introduce a radio-active substance that would remain for life. On the other hand, one can with safety use small quantities of Na^{24}, I^{131} and other short-lived radio-isotopes, since the quantities usable as a tracer dose would deliver, by the time they have disintegrated

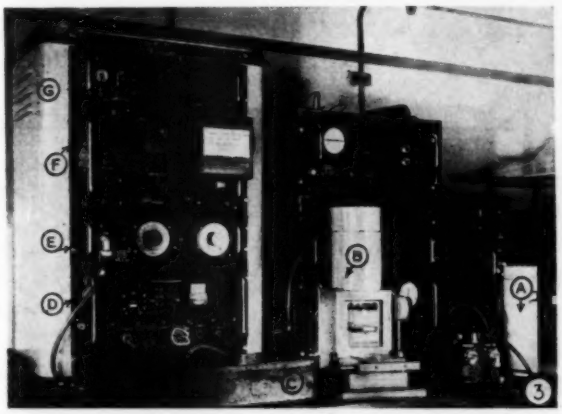


Fig. 3. A. Lead castle for liquid counter.
B. Lead castle for end-window counter.
C. Pre-amplifier.
D. Dynatron scaler.
E. High voltage supply for counter.
F. Timing unit.
G. Apparatus rack.

completely, less radiation than would be received in an ordinary X-ray picture taken for diagnostic purposes. In general, the shorter lived the radio-element, the safer it is for human beings; but it must have a long enough life to enable measurements to be made; and we in South Africa who have at present no facilities for making radio-isotopes in even microcurie quantities are debarred from using very short-lived radio-isotopes. As I shall mention later, the importation of Na^{24} (14.8 hours half-life) has now become possible, but probably nothing shorter-lived than this—at least until we have rocket-propelled transport from overseas! We can at the moment make extremely minute quantities of radio-elements, using our radium beryllium neutron source. A neutron generator is in the course of construction and this should give tracer amounts of some radio-isotopes. It is very much to be hoped that South Africa will at some time have her own source for the production of reasonable amounts, and a large demand from the medical profession would play its part in increasing our chances of getting the necessary equipment.

The most interesting application of radio-isotopes in medicine lies in diagnosis, and it is in this field that the most important developments are likely to take place. Some diagnostic applications are already to be regarded as routine. The time will certainly come when equipment for detecting and measuring radio-activity will be as ordinary a part of a medical laboratory as a microscope. For example, a method for the determination of circulating red cell volume has been worked out by Reeve and Veall.[2] A sample of the subject's blood is withdrawn and the washed cells incubated with P^{32}, which exchanges with the phosphorus in the cells so that they become labelled. They are re-injected, and after about 20 minutes a sample of blood is again withdrawn. The dilution of the radio-activity gives the total red-cell volume. It is considered that this method is considerably more accurate than the calculated volume estimated from the T1824 hematocrit method.

Na^{24} is a radio-element which lends itself to *in vivo* studies, as it emits penetrating gamma rays. Prinzmetal, Corday, Spritzler and Flieg,[3] in Los Angeles, have developed a technique which they call radiocardiography. Na^{24} is injected into one of the antecubital veins and the rate of uptake in the heart is measured by placing a gamma-ray counter over the praecordium. Normal curves have been established by the authors. Departures from the normal have been found to indicate heart disorders, sometimes in patients where the diagnosis had been missed. On the other hand, cases are quoted where normal curves indicated that an incorrect diagnosis of heart failure had been made. Subsequent examination of these cases revealed the true cause of the symptoms. The technique used by these workers has also been of value from a research point of view. Figure 4 shows (A) a normal curve and (B) a radiocardiogram of a patient sent as a normal control. Subsequent examination revealed a large mediastinal tumour pressing on the posterior aspect of the heart.

Radio-sodium is also being used in various parts of the world in the study of peripheral vascular disease. Smith and Quimby[4] have worked out a technique in which Na^{24} is injected into an antecubital vein, and its take-up at some point on a limb (e.g. the sole of the foot) is measured. Since sodium passes rapidly out of the blood vessels and into the extravascular fluid, the rate at which equilibrium is reached at any point gives information about the blood supply to that point.

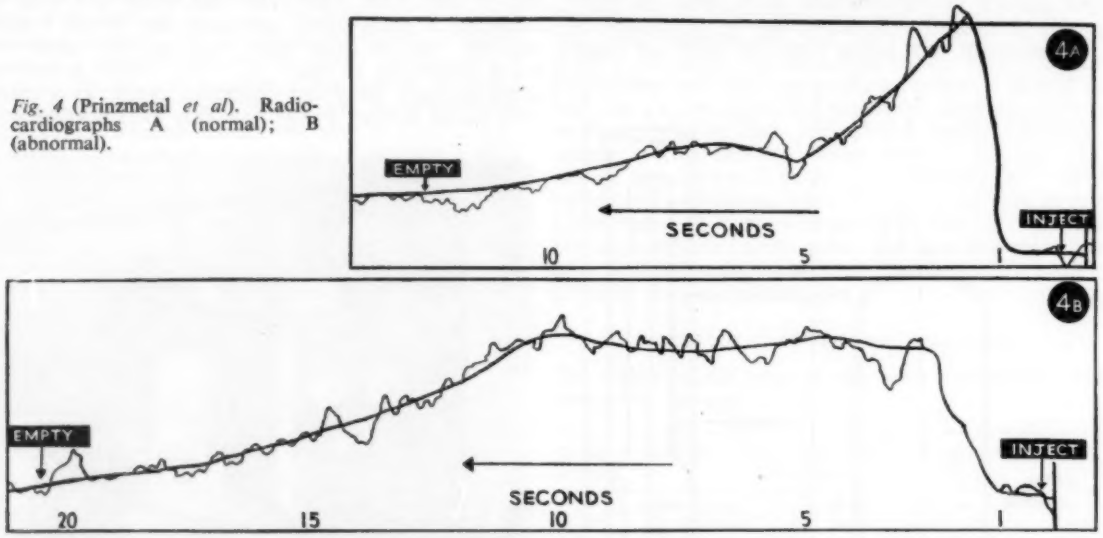


Fig. 4 (Prinzmetal *et al*). Radiocardiographs A (normal); B (abnormal).

Fig. 5 shows the type of curves which I have seen taken on a patient with an arterial block in one leg (the lower curve in the figure). The abovementioned authors state that they have found this method 'of special value in determining the advisability of persisting in conservative as compared to more radical local surgery, and particularly in determining the site of amputation at which healing might be expected'.

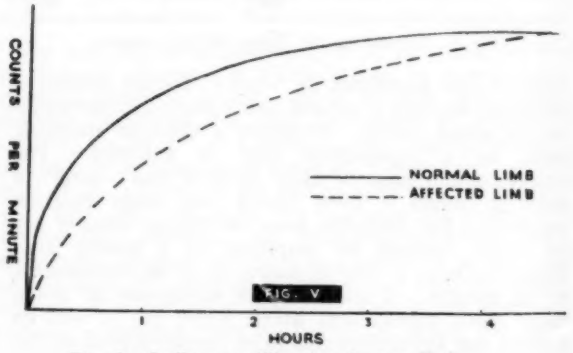


Fig. 5. Sodium equilibration in two limbs.

In South Africa we have already attempted some of the techniques mentioned. We have also had some experience of using radio-iodine as a diagnostic aid. It has been given as a tracer to several patients

with thyroid carcinomata,, with suspected or diagnosed metastases; the object being to find out whether the metastases were functioning as thyroid tissue, in which case radio-iodine could be used for radiation therapy. In one case a slight take-up of radio-iodine was found in a metastasis in the groin.

As radio-iodine is so strongly taken up by the thyroid it is being used a great deal as a form of radiation therapy in hyperthyroidism. Numerous successes are claimed and it undoubtedly offers a solution in inoperable cases, or in those which have already received as much external radiation as the skin can tolerate. It must be remembered, however, that as the major part of the administered iodine is excreted via the kidneys, therapeutic doses of radio-iodine will exert considerable radiation effects upon the gonads. Treatment of hyperthyroidism with radio-iodine should as far as possible be given only to patients past child-bearing age. These remarks do not of course apply to the use of I^{131} as a tracer where the dose of radiation is almost negligible. It has been used in this way as a diagnostic aid in suspected hyperthyroidism or other diseases of the thyroid, since norms for the take-up of iodine have been well established with the aid of radio-iodine.

Only very limited success can be claimed for the use of radio-isotopes given internally for radiation therapy. Reports from various centres are rather conflicting, but there is a definite tendency to regard radiophosphorus as the treatment of choice for polycythemia vera. Weinbren [8] and Weinbren and Morris, of Johannesburg, have undertaken a programme of treatment of several cases of polycythemia and of chronic leukaemia by this means, and one or two other radiologists have used radiophosphorus in selected cases. It will be some time, of course, before the value of the method can be assessed.

One important application which is not often mentioned is the use of suitable radio-isotopes as external gamma-ray sources. This is particularly applicable in South African hospitals, many of which complain of low stocks of radium. The most obvious choice to replace radium would be Co^{60}. There would be many advantages in using cobalt, which to my mind would outweigh the disadvantage of its relatively short half-life, 5.3 years. It can be made up in almost any form and it has no radio-active daughters, which make radium difficult to handle and which make leaky needles such a menace. The principal advantage is its low cost—£50 per curie, or less, as against £8,000 per gm. of radium. One could therefore replenish one's Co^{60} sources to make up for decay at a cost far less than the interest alone on an equivalent amount of radium. A most interesting possibility has been suggested by Dr. L. Cohen of the Johannesburg Hospital. We in South Africa have no radon available for permanent implants. It is possible to choose gamma-rayers of a somewhat longer half-life for this purpose, and Dr. Cohen [6] has estimated that a gamma-rayer of half-life of about 20 days should actually be more effective than radon for certain implants.

It is not possible to enumerate the many researches in medicine in which radio-isotopes have been an invaluable tool. Numerous reviews have appeared in journals and in books.[7-10] It would perhaps be of some interest to mention two research problems in which we at the National Physical Laboratory have participated. Dr. A. J. Clement, of the Witwatersrand University Dental School, was interested in the rate at which phosphorus is secreted in the saliva after its ingestion. Radiophosphorus presented an obvious means of dealing with this problem. We started by injecting small doses intravenously into volunteers, then collecting saliva samples and assaying them for radio-phosphorus. Secretion of the phosphorus was found

Fig. 6. Autoradiograph of chick embryo.

to have begun in samples collected two minutes after the beginning of the injection. Other volunteers swallowed radiophosphorus in enteric-coated capsules; here the first detectable radiophosphorus was found in samples collected within 15 minutes after swallowing. An attempt was also made to investigate the distribution of radiophosphorus in the salivary gland of a rat by the ' autoradiograph ' technique. This offers a means by which the distribution of a radio-active substance in a tissue can be determined. Histological sections containing radio-active material are placed in close contact with photographic film, and since the radiations blacken the emulsion, a radiograph is

obtained which shows the distribution of the material under investigation. Fig. 6 is an autoradiograph of a section from a chick embryo. Radiophosphorus was injected into the allantoic cavity of a fertile egg and two days later the embryo was removed and sectioned. Fig. 7 is the autoradiograph of a section of salivary gland from a rat which had received radiophosphorus.

An investigation which has given very interesting results was undertaken in collaboration with Dr. Bothwell of the Department of Medicine, Witwatersrand University Medical School. A patient with haemochromatosis

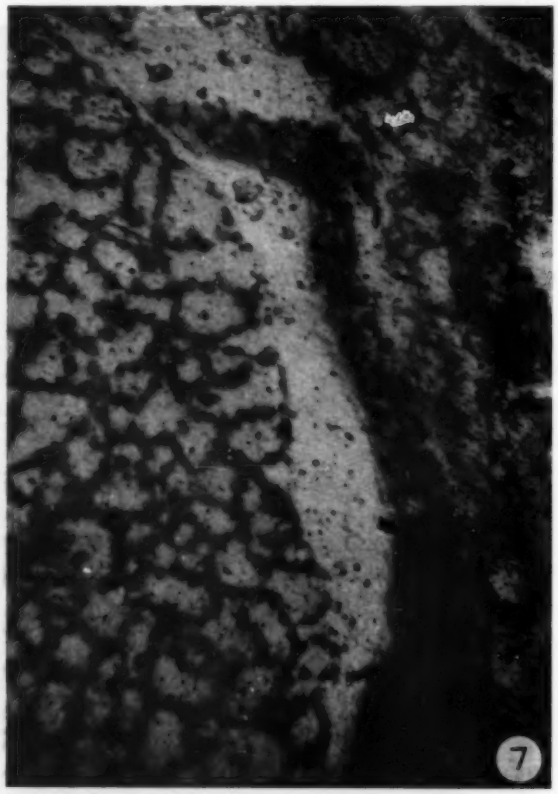
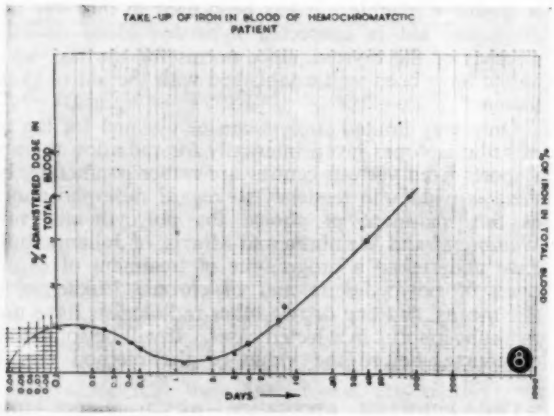


Fig. 7. Autoradiograph of rat salivary gland. Nuclei in acini can be seen clearly.

was given a tracer dose of radio-iron. The amount excreted was assayed; *in vivo* measurements were made over the heart, liver, kidney, spleen and thigh; numerous blood samples were taken and assayed for radio-iron. It was found that about 30% of the administered dose was absorbed, and for the most part was stored in the liver. A normal control showed no detectable radio-iron in any organ after three days. The curve of uptake of iron in the blood (Fig. 8) showed that within two hours 1.3% of the administered dose had been taken up by the plasma. The radio-iron in the total blood then dropped, and after 48 hours began rising steadily as the radio-iron was withdrawn from body stores and built into haemoglobin. By the eighty-sixth day about 4% of the administered dose appeared in the blood.

Those who may be interested in using radio-isotopes in their own researches will probably want to know something about the mechanism of getting what they need. The Council for Scientific and Industrial Research has been appointed as the only channel through which radio-isotopes may be imported. All applications are first scrutinized by a screening committee of that body. In general users must cover the costs, which are fairly high; though in research work in which the Council for Scientific and Industrial Research participates it may bear some or all of the costs. We obtain radio-isotopes from either the Atomic Energy Commission, U.S.A., or from the Atomic Energy Research Establishment, in England, and both bodies require that certain conditions be fulfilled if they supply radio-isotopes. I may say that up to the



present they have been extremely co-operative and have apparently been prepared to depend on our own Screening Committee.

The main cost of radio-isotopes is involved in handling charges and in air transportation. The latter is not high with pure beta-ray emitters, such as Ca^{45} or P^{32}; but radio-elements which emit gamma rays require a large amount of lead packing to ensure the safety of persons and of undeveloped film in the plane. As we must always order more than we need of shorter-lived isotopes and as the amount of lead needed increases with the amount of activity, the importation of therapeutic doses of I^{131} would be very expensive, and of Na^{24} almost prohibitive. A scheme has, however, been evolved by which radio-isotopes are to be carried in the wingtip of Skymaster aeroplanes. Here the distance from the body of the plane gives the protection heretofore provided by lead, and the cost of transporting large weights is eliminated. This brilliant scheme is largely due to Dr. E. C. Halliday[11] of the National Physical Laboratory. The arrangement will enable us to import the very useful but very short-lived Na^{24}. If 50 millicuries of this radio-element leaves Harwell we should have about 5 millicuries by the time

it gets to us, and this amount would provide many useful tracer doses within one or two days after its arrival.

ADDENDUM

The 'wingtip scheme' has been functioning smoothly since the beginning of 1950. Two batches of radio-sodium have been imported, the specific activity of the material on receipt being amply high enough for any of the established medical tracer uses of this radio-isotope. Radio-iodine is being imported regularly and is being used to a large extent in Johannesburg and in Pretoria as a diagnostic aid in thyroid conditions and for the treatment of hyperthyroidism. It has been used therapeutically in one case of carcinoma of the thyroid with functioning metastases.

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NEW PREPARATIONS AND APPLIANCES

POCKET NEBULISER OF ANTISTIN-PRIVINE

Ciba announce the introduction of a pocket nebuliser for the nasal administration of Antistin-Privine solution. Initially, it will be available for that solution only but it is later intended to have other solutions in this type of nebuliser. The apparatus is made of polythene and is unbreakable and non-refillable whilst being extremely economical In use. When the plastic cap is screwed on firmly it will not leak and it is of a suitable size and shape for carrying in the pocket or handbag. For the efficient production of a spray the nebuliser must contain a certain amount of air, hence, as issued, it is not completely filled with liquid. The fine mist ejected by the nebuliser increases the efficiency of the solution, which, for the eye, is still available in a dropper bottle.

The correct technique is as follows:—

Maintain the nebuliser in a vertical position whilst inserting the tip into the nostril. Place the top of the ball of the thumb level with the arrow on the label and *press firmly and sharply*; a fine mist will then be delivered from the nebuliser.

Suppliers in South Africa are Messrs. Sana Limited, P.O. Box 3951, Johannesburg.

VERENIGINGSNUUS : ASSOCIATION NEWS

SOUTHERN TRANSVAAL BRANCH

MINUTES OF THE GENERAL MEETING HELD ON 17 OCTOBER 1950

Present: Dr. Maurice Shapiro (in the Chair) and 58 members.

Obituary: Dr. Frank Levy.

New Members: Dr. Max Philip Shapiro.

Transfers: *To the Branch*: Dr. J. R. Duffield from Transkei Branch; Dr. L. E. Rayd from Cape Western Branch.

From the Branch: Dr. S. T. Seccombe to Transkei Branch; Dr. A. Lurie to Natal Coastal Branch; Dr. Ellen Rogoff to Natal Inland Branch; Dr. O. J. Verster to Northern Transvaal Branch; Dr. Mark Tombuk to Cape Western Branch; Dr. A. B. Horwitz to Griqualand West Branch.

Resignations: Dr. B. M. Sandler (proceeding overseas); Dr. J. A. Kay (permanently resident in Rhodesia); Dr. S. Jacobson (proceeding overseas).

A paper was read on: *Some Implications of Experimental Studies on the Reactions of Connective Tissues and Haemopoietic Organs, for our Understanding of Human Reticuloses and Blood Dyscrasias* by Prof. J. and Dr. T. Gillman.

Dr. T. Gillman stated that diseases could actually be divided into various types:—

1. Rheumatic-like diseases including periarteritis nodosa and the collagen diseases.

2. Sclerosing diseases, e.g. arthritis, nephrosclerosis, atherosclerosis, tuberculosis, syphilis and silicosis.

3. The blood dyscrasias, such as pernicious anaemia, haemolytic diseases, leukaemias and lymphomata, etc.

He drew the attention of the meeting to the fact that there was the possibility of many seemingly unrelated diseases being actively related to each other. In the experiments which he and his brother had carried out, rats were given injections of 1 c.c. 1% trypan blue at fortnightly intervals until the animal died. He then showed slides of the effect of the trypan blue on the organism at various stages after injections. These slides demonstrated the various changes that could be found in the blood, and in addition, the different kinds of tumours which developed in the body. Malformations were also found in the offspring of those animals treated with the trypan blue. Gross malformations of the skeleton occurred. Haemolytic anaemia of the new-born was found as was also nephrosclerosis. In those that managed to survive early infancy, neoplasms occurred later. The offspring were all found to live a shorter time than normal. In the offspring of the offspring a high incidence of pathological conditions was also found.

Prof. J. Gillman then discussed the mechanism involved in causing this wide range of diseases, and he ultimately came to the conclusion that the same stimulus can have different effects on the same type of animal, and that different stimuli could, under certain conditions, bring about the same type of effect.

A great deal of discussion ensued, in which Drs. Bloomberg, Cohen, Morris, Stein, Pratt-Johnson, M. Weinbren and Schneider took part.

The Meeting closed with a very hearty vote of thanks to the two lecturers for the intensely interesting and stimulating evening they had provided.

T. Schneider,
Honorary Secretary.

PASSING EVENTS

At an interesting ceremony held at the University of Pretoria on 2 November, a colour film of the tour of final year medical students to Southern and Northern Rhodesia during July 1950 was shown. The tour was undertaken in connexion with the study of tropical diseases, the film having been sponsored by Messrs. Westdene Products (Pty.) Limited of Johannesburg.

The film was presented to the University by the sponsors and an appropriate speech was made by Mr. Reichenberg (of Westdene Products (Pty.) Limited) to mark the occasion.

This is a most valuable step taken in the development of medical education in the Union.

W.H.O. Regional Office for Africa: Chief Appointed

General Francois Daubenton of the Netherlands has been appointed Chief of the World Health Organization's Office for Africa.

The newly created WHO Office for Africa will be situated at Geneva headquarters pending establishment of a regional organization. Other WHO Regional Offices are already operating in New Delhi, for Southeast Asia; Alexandria, for the Eastern Mediterranean Area; a temporary office in Hong Kong for the Western Pacific; and a temporary office for Europe at Geneva. The Pan American Sanitary Bureau in Washington, D.C., serves as WHO Regional Office for the Americas.

General Daubenton was formerly a Public Health Consultant with WHO at Alexandria and headed the WHO Mission to Ethiopia. He was born at Rotterdam in 1888 and studied at Utrecht, Lausanne, London and Johannesburg.

Before joining WHO, he directed medical services in the Royal Netherlands Army with the rank of Lieutenant-General. Earlier, he was Deputy Chief of Staff of the Netherlands Military Government.

Before the war, General Daubenton spent more than 20 years in Africa, where he was Chief Medical Officer for a large gold-mining group, responsible for the establishment and supervision of Native hospitals. Later he held other health posts in which he acquired a wide knowledge of African health problems.

* * * *

The Institute of Dermatology, a member of the British Post-Graduate Medical Federation (University of London) and based on the St. John's Hospital for Diseases of the Skin, Lisle Street, Leicester Square, London, W.C. 2, has issued a brochure setting out the educational facilities available for those wishing to attend lecture courses, clinical instruction, etc.

Copies of the brochure have been sent to the Universities of Cape Town, Johannesburg and Pretoria.

OFFICIAL ANNOUNCEMENT

Federal Council

The Federal Council of the Medical Association of South Africa resolved at its meeting held in Johannesburg on 14 October 1950, that officials and dependants of officials from the High Commission territories who seek medical treatment in the Union should be afforded such treatment at Medical Aid Society rates, provided that the High Commission Government makes itself responsible for the fees.

A. H. Tonkin,
Medical Secretary.

Medical House,
Cape Town.
23 November 1950.

AMPTELIKE AANKONDIGING

Federale Raad

Op die vergadering gehou te Johannesburg op 14 Oktober 1950 het die Federale Raad van die Mediese Vereniging besluit dat amptenare en afhanklikes van amptenare wat in gebiede van die Hoë Kommissarisse werksaam is en wie mediese behandeling in die Unie verlang sulke behandeling teen Mediese Hulpvereniging tariewe behoort te ontvang, op voorwaarde dat die Regering van die betrokke Hoë Kommissaris self aanspreeklikheid vir die fooie aanvaar.

A. H. Tonkin,
Mediese Sekretaris.

Mediese Huis,
Kaapstad.
23 November 1950.

REVIEWS OF BOOKS

Analgesia in Labour

Analgesia for Normal Childbirth. By E. H. Seward, M.A., B.M., B.Ch. (Oxon.), D.A., D.Obst., R.C.O.G. (Pp. 19 + vii with 4 Figures. 2s.) Oxford: Blackwell Scientific Publications, Limited. 1950.

Contents: 1. Introduction. 2. The Pain of Labour. 3. Method of Pain Relief. 4. Conduct of Pain Relief. 5. Nitrous-Oxide/Air Apparatus. 6. Care of the Apparatus. 7. Checking the Apparatus before Use. 8. Observations During Nitrous-Oxide/Air Administration. 9. Causes of Failure of Analgesia. 10. Contra-Indications to Nitrous-Oxide/Air Analgesia. 11. Rules of the Central Midwives Board Relating to Analgesia.

Dr. Seward, who is research assistant in the Nuffield Department of Anaesthetics at the Radcliffe Infirmary, Oxford, has written a valuable and concise account of how to relieve pain in labour, with the aid of nitrous oxide.

The material in this little pamphlet should be read not only by every accoucheur but can also safely be recommended to the attention of every intelligent mother. It will be particularly useful to midwives.

The preface by Professor Macintosh who is Nuffield Professor of Anaesthetics at the University of Oxford commends Dr. Seward's pamphlet in the highest terms.

Murder, the Prepsychotic Personality and Legal Responsibility

Trial of Peter Griffiths. Edited by George Godwin. (Pp. 219 with illustrations. 15s.) London, Edinburgh, Glasgow: William Hodge and Company Limited. 1950

Contents: 1. Introduction. 2. Chronological Table. 3. The Trial: First Day—Friday 15 October 1948; Evidence for the Prosecution. 4. Second Day: Monday 18 October 1948; Evidence for the Defence. 5. Evidence in Rebuttal for the Prosecution. Appendices I, II and III.

Twenty-two-year-old Peter Griffiths, after drinking fairly heavily on 14 May 1948, went by taxi to the neighbourhood of the Queen's Park Hospital in Blackburn. He made his way with stealth and caution through a break in the hospital wall to the Babies' Ward. (Griffiths knew the lay-out of the hospital and its surroundings very intimately).

After taking off his shoes he made his way through this Ward in his stockinged feet, leaving clear impressions on the highly polished floor. He took from her cot a little girl not yet four years old and carried her off to a deserted part of the grounds, some 200 to 300 yards away. There he raped the child, afterwards killing her by dashing her head against a nearby wall, and returned to the hospital to put on his shoes before going back home. Griffiths subsequently lied about his taxi journey to the hospital and about the time of his return to his parents' home.

His father had been certified at one time as a case of paranoid dementia praecox and, although discharged, was regarded by his neighbours as being 'queer'.

Peter Griffiths himself had fallen on his head at the age of six and had been sick thereafter with vomiting following a probable disturbance of consciousness. As a child Peter had also spent two years as an in-patient for incontinence of urine in the very hospital from which he stole the deceased.

There was no attempt to deny the commission of the crime. The defence rested on the allegation that the accused was insane at the time he raped and killed the child.

The record of this trial, therefore, raises a most important issue. Insanity is a form and degree of mental disorder for which lawyers have created an artificial description in order to satisfy the human passion for precise definition and to make easy a decision about responsibility for an act. From the lawyer's point of view, the principles of determining criminal responsibility in these circumstances are enshrined in what have come to be known as the M'Naghten rules. According to these rules it becomes relevant to discover whether the accused suffered at the time from a disease of the mind which resulted in a defect of reason such that he did not know what he was doing; or, if he knew what he was doing, that he did not know it was wrong.

A very valid criticism of these rules is their assumption that human behaviour is determined by reason only. It is to-day readily conceded that emotional factors may play possibly an even greater part in determining behaviour and that the

aetiology of criminal tendencies probably derives very significantly from the early social environment of the delinquent.

The defence consisted mainly of the medical evidence called in support of the view that Peter Griffiths was a case of early schizophrenia. Dr. Grant, medically qualified for some 35 years at the time of the trial, and a man who had specialized nearly all his life in mental diseases and who had spent the past 17 years employed at the Whittingham Mental Hospital, stated categorically (p. 134): 'I think this man is an early case of schizophrenia'.

It is not surprising to find that the Crown, in calling evidence in rebuttal for the Prosecution, obtained from a Dr. Brisby, the Principal Medical Officer in His Majesty's Prison Service in Liverpool, and with less than two years' experience in a County Mental Hospital, the contrary view: 'From my observation and examination of the man during the period he has been under my care, I have found no evidence of any disease of the mind which would prevent him from either knowing what he was doing, or that it was wrong' (p. 157).

The Prosecution's cross-examination of Dr. Grant is a masterly performance. There was no evidence that the accused was hallucinated or even deluded. It was generally admitted that he was a solitary kind of youth and it was recognized that the disruption of a love affair a few days before the crime together with the heavy bout of drinking might have precipitated a manic crisis. In the face of premeditation, stealth, caution and a remarkably clear recollection of many details of the events which took place, the accused's Counsel found it difficult to satisfy reasonable men that a maniacal frenzy occurred just at the moment before he raped and killed the child—a frenzy which completely and suddenly wore itself out after the killing and left the accused in a position to try to cover up his tracks with lies about his movements that night.

The crux of the problem is his responsibility for an act which, by its very nature, strongly suggested a degree of mental disorder almost satisfying the legal concept of insanity. This matter is extremely ably reviewed by the Editor in an excellent introduction to the *Trial* in which the suggestion is made that valuable information about 'Griffiths' probable mental and emotional condition at the time of the crime could have been demonstrated only by the E.E.G. technique' (p. 32).

It would undoubtedly be of great interest to know what the accused's brain-wave pattern looked like, but it is doubtful if it would have made it any easier for the Court to decide the crucial issue of legal responsibility. Moreover, there is no characteristic E.E.G. pattern for schizophrenics; the Editor appears to be under a distinct misapprehension about this. It would probably generally be agreed that the accused had a schizoid temperament, but it is difficult to see that the case for early but definite schizophrenia was made out.

In the event, there can be little doubt that the Jury's finding that Griffiths was guilty was a correct one. It is also of interest that, when he was asked if he had anything to say why the Court should not pass sentence of death upon him, the prisoner replied 'No'. This behaviour is entirely in keeping with his expressions of remorse at the time of his arrest and the hope he uttered that he would get what he deserved.

In the view of the Jury and the Court, therefore, Peter Griffiths was legally responsible for what he had done; but there can be no doubt that his personality was a mentally and emotionally disordered one.

The legal distinctions are clear cut. The accused is either insane or not. The law makes no provision for the infinite gradations of behaviour between these two extremes. There seems room for the return of a verdict which will allow the Court to find an accused person guilty, but mentally disordered, although not insane by absolute and arbitrary legal criteria. Such a verdict might strengthen the hands of the responsible authorities to stay an execution, after conviction, in circumstances such as those surrounding the case of Peter Griffiths.

After all, a good case could have been made out for the view that Peter Griffiths had a prepsychotic personality; that the complex of behaviour, culminating in his dreadful crime, arose out of a mentally and emotionally disordered prepsychotic condition, precipitated by the events *preceding* his hiring of the taxi to go to the hospital; and that the accused was inescapably caught up in a mesh of events which led inexorably to the dreadful cathartic climax of rape and murder. If his case had been presented in this perspective, Dr. Grant would not have found himself in the absurd and futile position of trying to persuade a Jury that the accused was mentally normal up to the time just before the rape was committed, and that he regained his normality immediately after the killing.

Although the medical reader will naturally have a primary interest in the thorough manner in which the whole problem of insanity was reviewed in this case, he will find much equally fascinating in the remarkable procedure whereby the accused was discovered and identified by means of the fingerprints which he left upon a Winchester bottle and the footprints on the polished floor of the Babies' Ward. The net to discover the murderer was cast very wide and involved the inspection of some 10 million fingerprints, in England and abroad (including South Africa).

In all respects this is a most excellent addition to the *Notable British Trial Series.*

MURDER BY NEGLECT: THE VELPKE BABY HOME WAR CRIMES

War Crimes Trials Vol. VII: The Velpke Baby Home Trial. Edited by George Brand, LL.B. With a foreword by Prof. H. Lauterpacht, K.C., LL.D., F.R.A. (Pp. 356 + liv, with illustrations. 18s.) London, Edinburgh and Glasgow: William Hodge and Company, Limited. 1950.

Contents: 1. Foreword. 2. Introduction. 3. The Court and Counsel. 4. The Trial: First Day—Wednesday 20 March 1946. 5. Evidence for the Prosecution. 6. Second Day—Thursday 21 March 1946. 7. Third Day—Friday 22 March 1946. 8. Fourth Day—Saturday 23 March 1946. 9. Fifth Day—Monday 25 March 1946. 10. Evidence for the Defence. 11. Sixth Day—Tuesday 26 March 1946. 12. Seventh Day—Wednesday 27 March 1946. 13. Eighth Day—Thursday 28 March 1946. 14. Ninth Day—Friday 29 March 1946. 15. Tenth Day—Saturday 30 March 1946. 16. Eleventh Day—Monday 1 April 1946. 17. Twelfth Day—Tuesday 2 April 1946. 18. Thirteenth Day—Wednesday 3 April 1946. Appendices I and II. Index.

This trial concerns the criminal actions of certain persons in Germany who were concerned with the care of newly-born infants of female Polish and Russian workers deported to Germany to assist the agricultural output for the German war effort. The German authorities were of the opinion that the pre-natal and post-natal condition of these female workers interfered with their working capacity. Consequently, a Home was established (in 1944) for the reception of these infants who were taken away, if necessary by force, as soon as possible after they were born, with the object of allowing the mother to continue her work without interruption.

Three corrugated iron sheds in a disused quarry were selected as the Home which was known by the local people as the 'Velpke Barracks'. From May to December 1944, 96 infants died in these Barracks and 14 who survived were taken away to another home, thus not falling within the scope of the Velpke trial.

The babies came to the Home warmly clad and in good health, but in a few days 'they were starving, bitten with bugs and covered with sores through lying in urine-soaked bedding unattended, and within a few days they were dead. The mothers were frequently not informed of the death, and for a very large number it was only when they arrived at the Home that they found the child already dead, or, in some cases, not only dead but buried'.

Not only was there compulsory separation of children from parents, but subsequently the parents were denied access to their own infants and great secrecy surrounded the conduct of the Home.

The Prosecution alleged 'that these children were never meant to live, but by a system of wilful neglect consisting of improper feeding, premature separation, dirty conditions, insufferable heat with shut windows and a stove in a corrugated iron shed in summer, lack of attention in the changing of bedding and clothing and treatment, bed-sores, lack of medical attention, except to sign death certificates, lack of trained nurses, no running water, insufficient hygienic precautions with bottles, sour milk, and too full a diet and failure to nourish either by passing it through the body by vomiting or diarrhoea; by all these things it was intended that they should die, and die they did'.

It is incredible that so-called human beings could have their sense of moral values debased to the extent revealed in this trial.

A Dr. Demmerich was sentenced to imprisonment for 10 years and the matron of the Home received 15 years' imprison-

ment. The accused Hessling and Gerike were sentenced to death by hanging.

It is difficult to believe that the events described actually took place. It is well that the evidence of these terrible crimes should be recorded. However unpleasant the task, it is desirable also that medical practitioners particularly should read these records. They will give those of us who were far removed from the scene of the atrocities at the time, a clearer understanding of the need, after many centuries, to devise a modern Hippocratic oath.

HANDICAPPED CHILDREN

Children with Mental and Physical Handicaps. By. J. E. Wallace Wallin, Ph.D. (Pp. 549, with 34 illustrations. 42s.) London and New York: Staples Press, 1950. (South African Representative: Mr. Paul Kosten, P.O. Box 4782, Cape Town).

Contents: 1. Introduction. 2. Multiple Definitions of Mental Defectiveness. 3. Psychological Concepts and Theories of Mental Defectiveness. 4. The Relationship between Mental Deficiency and Mental Disease. 5. The Definition of the Backward Child—The Dullard or Dull Normal. 6. Classification according to Psychological Characteristics. 7. Classification according to Educability and Socio-Vocational Competency. 8. Classification according to Etiology. 9. Classification according to Special Clinical Types—Endocrinopathic Disorders. 10. Cretinism (Myxedematous Infantilism). 11. Mongolism. 12. Growth Anomalies related to Endocrine Disturbances. 13. Growth Anomalies related to Biochemical or Metabolic Disturbances or Nerve Degenerations. 14. Epileptic Seizures in Children. 15. The Causation and Treatment of Epilepsy. 16. Children afflicted with Encephalitis. 17. The Orthopedically Disabled: Cerebral Palsy. 18. The Orthopedically Disabled: Poliomyelitis. 19. Microcephaly. 20. Hydrocephalus (or Hydrocephaly). 21. Syphilitic Brain Defects. Index.

Teachers, social workers, psychologists, doctors and all those who have, as part of their work, to deal with handicapped children should find this volume a great help. The author has written his book in such a way that it is eminently suitable for those wishing to study a certain aspect of the problem only. Separate chapters are devoted to classifying the problem along the lines of educability, socio-vocational competency, etiology, psychological characteristics, and clinical types.

The numerous case histories are interesting and the illustrations useful for those not well acquainted with the defects mentioned.

The bibliographical references are up to date and will be of great use to those wishing to pursue any of the topics further.

The author, in discussing the various grades of mental defectiveness and the exact meaning of this term, warns against the limitations of the I.Q. as a single measure of brightness or dullness in any one case. An interesting discussion of the quantitative and qualitative theories of mental defectiveness is given and here, as in other chapters of the book, all the arguments together with the criticisms are particularly clearly set out.

In considering the nature of the causal relationship between mental defect and mental disorder, the author discusses the data gathered and the conclusions drawn, although he goes on to point out that the final verdict on this question cannot yet be given.

The particularly interesting manner in which the subject has been presented serves to make it a valuable contribution to the libraries of those dealing with handicapped children.

THE SPRINGS OF CONDUCT

The Springs of Conduct: A Neuro-Psychological Study. By Sir John Parsons, *C.B.E.*, F.R.C.S., F.R.S. (Pp. 104 + viii. 7s. 6d.) London: J. & A. Churchill Limited, 1950.

Contents: 1. Historical Introduction. 2. Comparative Psychology. 3. Physiology. i. From Reflex to Concept. ii. Comparative Psychology and Physiology. iii. Experimental Physiology and Pathology. 4. The Integration of the Individual. 5. The Role of Reason. 6. The Tyranny of Emotion. 7. The Influence of Neurology on Psychology. Conclusion. Notes.

It is probably fortunate that, at this awkward stage of Man's social development, there have been made discoveries about his psychological structure and bodily functioning which will help him to understand the origins of his behaviour. For the great problem of human development is how to tame and modify those complex and primitive forces which hamper and threaten peaceful existence.

Sir John Parsons, with commendable courage, attempts to organize the discoveries made by the natural scientists concerning Man and his nature. The task he undertakes is, therefore, largely a philosophical one. Unlike a few of his scientific peers, however, Sir John produces no mysticism. Early in the book the reader is reminded that man is an animal, and Sir Charles Sherrington is quoted: 'It is strange but true that one among the animals should have been led to fancy itself so different from the rest as to forget that it was an animal'. Man is the animal at the head of the primates and cannot escape habits of mind which cling closely to habits of body.

The intimate relationship which body has to mind is explored, and, with skill and persuasiveness, the known facts of cerebral functioning are discussed. Emotional factors are closely associated with somatic activities; the hormonal secretions are profoundly important for normal living, and are in turn controlled by the hypothalamus. The highest levels for consciousness might be in the frontal lobe. The representation of various functions in the cerebral cortex have been localized, but Penfield Wilder has warned that although a given response follows point stimulation, it is not to be concluded that functions are localized in these points, for the stimulation activates a set of neurone connexions through which many other neurone connexions may pass. The ability to chart the electrical responses of the brain with the electro-encephalograph is of great importance to both physiology and psychology.

Man, in Elliot Smith's opinion, has achieved dominance over the other animals because he has adopted the upright posture and perfected his vision; but Man has, in addition, an intelligenee which has been raised to the status of reason, and through the development of conceptual thought he has immeasurably extended his dominance over the springs of conduct.

MANSON'S TROPICAL DISEASES

Manson's Tropical Diseases. Edited by Sir Philip H. Manson-Bahr, *C.M.G., D.S.O.*, M.A., M.D., D.T.M. and H. Cantab., F.R.C.P., Lond. (Pp. 1136 + xiv. With 17 colour plates, nine half-tone plates, 412 figures in the text, eight maps and 29 charts. 13th ed. 45s.) London: Cassell and Company, Limited. 1950.

Contents: Section 1. Fevers. Section 2. Vitamin Deficiency Diseases (Avitaminoses). Section 3. Abdominal Diseases. Section 4. Infective Granulomatous Diseases. Section 5. Diseases of the Central Nervous System. Section 6. Tropical Venereal Diseases. Section 7. Tropical Skin Diseases. Section 8. Local Diseases. Section 9. Animal Parasites and Associated Diseases. Section 10. Diseases due to Poisons, Including Snake Bite, and Infection with Dipterous Flies and Leeches. Section 11. Special Subjects. Appendix.

'Manson-Bahr' is a book which is a *sine qua non* for any practitioner working in the tropics or sub-tropics and the new edition is pleasing because it is so up to date. It is refreshing to see a standard textbook change so much from edition to edition, and in fact owners of the 11th edition would hardly recognize the 13th edition as the same book.

The tremendous advances which have been made in recent years in general medicine also apply to tropical medicine, which is, however, not without advances of its own. To quote but a few dealt with in the new volume, one may mention the effect of Paludrine on the pre-erythrocytic phase of malaria. The pre- and exo-erythrocytic phases of this condition are dealt with in the appendix on medical protozoology. In the treatment of the rickettsial diseases both PABA and Chloromycetin are discussed, as are the use of folic acid in the treatment of sprue and the use of the sulphones in leprosy. Mention is made of the use of Aureomycin in amoebic dysentery.

If one could level any criticism at this book it is the lack of a bibliography. The author has been most meticulous in giving credits to those responsible for various theories, but nowhere may one find the actual references. Though some may consider that this book is primarily for students, many a senior man will refer to it and would like to be able to check the original article.

We in South Africa are seeing more and more of diseases previously considered as purely tropical and for this reason every practitioner should have this book on his shelves.